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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: Docket No. 99D-2635 - Guidance for Industry: ANDAs: Blend Uniformity Analysis

The National Association of Pharmaceutical Manufacturers (NAPM) appreciates the opportunity to comment on the document, " Guidance for Industry -- ANDAs: Blend Uniformity Analysis" [Docket No. 99D-2635]. These comments represent the consensus of leading manufacturers of generic drug products.

NAPM feels that the issuance of a guidance on blend uniformity analysis is premature and strongly recommends that the draft guidance be withdrawn.

As mentioned in p. 2 of the guidance, *FDA intends to seek support of the Product Quality Research Institute on blend uniformity. The guidance will be updated based on the outcome of any research.* The members on the Drug Product Technical Committee of PQRI represent the major segment of the pharmaceutical industry and includes representation from innovator (brand) and generic drug product manufacturers, FDA and the academic community. This expert panel recommended, blend uniformity 'analysis as a top research priority., The expert panel realizes that more research is needed to determine, the utility of blend uniformity analysis. NAPM concurs with the PQRI Drug Product Technical Committee that more research, is needed and thus NAPM feels. that FDA should not implement a guidance before the scientific foundation, for such a guidance has been established.

There are several 'other issues concerning blend uniformity analysis that we wish to discuss:

- When is blend uniformity analysis required?
- What type of sampling/methodological approaches should be used to assure that the results obtained accurately reflect a measure of blend uniformity?

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- Can extensive and representative tablet/capsule content uniformity data be used to evaluate blend uniformity?

- Should all complex drug products such as modified release products have more stringent blend uniformity analysis requirements than immediate release solid oral drug products?

When is blend uniformity analysis required?

There has been an inconsistency in the Agency's application of blend uniformity testing requirements for solid oral dosage forms. Blend uniformity should be a part of process validation. Therefore, the continual use of blend uniformity analysis on every production batch is unwarranted. Since the blend uniformity analysis is a validation test, specifications for blend uniformity should not be a part of the Abbreviated New Drug Application. Rather, blend uniformity analysis should be a District compliance issue.

Recommendation: We would encourage the Agency to reevaluate their policy on setting specifications for blend uniformity and consider blend uniformity to be part of process validation, which would then become a District compliance issue. In addition, firms should be allowed to eliminate routine blend uniformity analysis in existing approved ANDAs by submitting a CBE along with supporting data.

What type of sampling/methodological approaches should be used to assure that the results obtained accurately reflect a measure of blend uniformity?

Present sampling techniques, both with the blend and the QC laboratory prevent some products from achieving true results. Small sample sizes using a 'thief' may result in displacement of some particles so that the sample obtained is not truly representative of the blend. In addition, the QC laboratory is not allowed to mill the sample that is removed from the blend so that the assay results on an aliquot of the sample may not accurately reflect the homogeneity of the sample.

Recommendation: During process validation, the appropriate sampling technique should be determined. The batch should be completely compressed or encapsulated and data comparisons are then analyzed statistically. Larger samples may be taken from the blend to truly test for blend uniformity (versus content uniformity). Moreover, the sample for the QC laboratory may be milled prior to analysis so *QC* does not introduce an additional error. Alternatively, for some drug products, it may be appropriate to analyze the entire sample. The requirement of resampling for the blend needs to be loosened since there are many errors introduced into the sampling technique and in the QC testing technique.

Can extensive and representative tablet/capsule content uniformity data be used to evaluate blend uniformity?

The assay of the finished drug product is the most accurate measure of dosage form uniformity. The USP has long recognized the need for content uniformity analysis and describes in Section <905> the procedures for Uniformity of Dosage Units. The homogeneity of the finished drug product and the precision in manufacturing each dosage unit are most important for the safe and efficacious use of the product.

Recommendation: Extensive and representative tablet/capsule content. uniformity data obtained during process validation should be used to evaluate blend uniformity.

Should all complex drug products such as modified release products have more stringent blend uniformity analysis requirements than immediate release *solid* oral drug *products?*

The complexity of complex drug products depends upon the formulation and the method of manufacturer of the product. The manufacture of some complex drug products is relatively simple and well-controlled. For some complex drug products such as modified and extended release drug products, blend uniformity analysis is similar to immediate release drug products.

Recommendation: Blend uniformity analysis for complex drug products should not automatically be considered differently. We would like the Agency to provide a rationale for having more stringent blend uniformity requirements for complex drug products.

NAPM is the national trade organization representing manufacturers, distributors and repackagers of generic multisource prescription drugs, OTC drugs, dietary supplements and veterinary drugs. The organization prides itself in serving the needs of its members and has been heavily involved in legislative, legal, regulatory and technical issues.

We thank you for the opportunity to submit our comments. We hope that our comments are clear and welcome any questions that you may have.

Sincerely,

Leon Shargel

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cc: Devinder S. Gill, Ph.D.